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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,558	09/02/2005	Jorg Hacker	H&U122	9541

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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,558	HACKER ET AL.	
	Examiner	Art Unit	
	Michele K. Joike	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed February 25, 2010. Claims 1-6 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed September 1, 2009 that is not addressed in this action has been withdrawn.

Response to Arguments Concerning Claim Rejections – 35 USC § 103 (a)

Applicant's arguments filed February 25, 2010 have been fully considered but they are not persuasive.

The following grounds of traversal are presented:

Applicants have deposited a plasmid-free strain of DSM 6601 as suggested by the Examiner. However, upon further review, the Examiner does not believe that the deposited strain obviates a 35 U.S.C. 103(a) rejection. There is no indication that the references teaching the parent strain, DSM 6601, and a method of curing strains, would not lead to the same strain as the deposited strain. Other than the strain being cured of plasmids pMut1 and pMut2, there is nothing noted about the deposited strain that would distinguish it from any DSM 6601 strain cured of pMut1 and pMut2.

However, the combined references fail to teach curing of more than one plasmid. Therefore, a new 103(a) rejection is made below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uraji et al, in view of Blum-Oehler et al, Trevors et al and in further view of Gasson et al.

Uraji et al (Genes Genet. Syst. 77: 1-9, 2002, specifically p. 3, including figure 1 and p. 7) teaches a curing method wherein bacteria are transformed with a plasmid containing an introduced sacB gene and an introduced kanamycin resistance cassette. The bacterium already contains a second plasmid (without the sacB gene). The bacteria is then cured of both plasmids by culturing the cells overnight in LB supplemented with sucrose (also called saccharose), and then were grown on media supplemented with kanamycin. Uraji et al do not teach the sacB gene on the second plasmid, because the plasmid is already present in the cell. However, they do teach that sacB should be in a plasmid being introduced into the cell that is being cured. Therefore, if two plasmids are being introduced into the cell, it would follow that both plasmids would contain the sacB gene in order to cure the cell. In claim 6, the steps are the reverse of the method steps taught by Uraji et al. First, the transformed bacteria are cultivated on plates containing the antibiotic, and then subsequently on plates containing saccharose. As stated in MPEP 2144.04 (IV)(C), selection of any order of

performing process steps is prima facie obvious in the absence of new or unexpected results.

> C. Changes in Sequence of Adding Ingredients
>
> *Ex parte Rubin* , 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render *prima facie* obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is *prima facie* obvious.).

However, Uraji et al do not teach the DSM 6601 strain, or the pMut plasmids, or curing more than one plasmid.

Blum-Oehler et al (IDS ref., specifically pp. 59) teaches the E. coli strain, DSM 6601, which is also called Nissle 1917, which contain the pMut1 and pMut2 plasmids. However, they do not teach curing plasmids.

Trevors et al (FEMS Microbiol. Reviews 32: 149-157, 1986, specifically p. 149) teaches curing bacteria of plasmids.

Gasson et al (J. Bac. 154(1): 1-9, 1983, especially, p. 1, table 1 and figure 2) teaches curing a Streptococcus strain of five plasmids.

The ordinary skilled artisan, desiring to have a plasmid-free clone of DSM 6601, would have been motivated to combine the teachings of Uraji et al teaching how to cure bacteria of plasmids using the sacB gene with the teachings of Blum-Oehler et al teaching the DSM 6601 strain because Trevors et al teach that it is desirable to cure

bacteria of plasmids because it allows for a direct comparison of cells with and without plasmids, and Gasson et al teach that a strain having more than one plasmid can pose problems in assignment of suspected plasmid-encoded phenotypes to individual molecules. It also complicates the analysis of plasmid transfer experiments, and the molecular study of individual plasmids from the complement. One further would be motivated to cure DSM 6601 because Blum-Oehler et al teach that DSM 6601 is useful as a probiotic drug against intestinal disorders and diseases, and, as taught by Blum-Oehler et al, their method is a much safer way of curing as it essentially has no effect on the host chromosome. It would have been obvious to one of ordinary skill in the art because Blum-Oehler et al teach that the plasmids (pMut1 and pMut2) are cryptic plasmids and have no apparent benefit to their host. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 2-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uraji et al in view of Blum-Oehler et al, in view of Trevors et al and Gasson et al and in further view of Alexeyev et al.

Applicants teach a method of preparing plasmid-free clones (curing) by a) introducing a resistance gene into plasmids pMut1 and pMut2, b) introducing the sacB gene into the plasmids obtained in step a), c) introducing the plasmids obtained in step b) into the E. coli strain DSM 6601 and cultivating the strain under conditions in which

the naturally occurring plasmids pMut1 and pMut2 are displaced by the plasmids obtained in step b); and d) cultivating the clones obtained in step c) that substantially only permit the growth of bacteria that lack the sacB gene. pMut1 contains the tetracycline resistance cassette, and pMut2 contains the kanamycin resistance cassette. In claim 6, the bacteria are transformed with plasmid pMut1, marked with a tetracycline resistance cassette and the sacB gene, and cultivated on plates containing tetracycline and subsequently on plates containing saccharose, and that after elimination of plasmid pMut1 in the first step elimination of plasmid pMut2 takes place by cultivation on kanamycin plates and further cultivation on saccharose plates.

Uraji et al (Genes Genet. Syst. 77: 1-9, 2002, specifically p. 3, including figure 1 and p. 7) teaches a curing method wherein bacteria are transformed with a plasmid containing an introduced sacB gene and an introduced kanamycin resistance cassette. The bacterium already contains a second plasmid (without the sacB gene). The bacteria is then cured of both plasmids by culturing the cells overnight in LB supplemented with sucrose (also called saccharose), and then were grown on media supplemented with kanamycin. Uraji et al do not teach the sacB gene on the second plasmid, because the plasmid is already present in the cell. However, they do teach that sacB should be in a plasmid being introduced into the cell that is being cured. Therefore, if two plasmids are being introduced into the cell, it would follow that both plasmids would contain the sacB gene in order to cure the cell. In claim 6, the steps are the reverse of the method steps taught by Uraji et al. First, the transformed bacteria are cultivated on plates containing the antibiotic, and then subsequently on plates

containing saccharose. As stated in MPEP 2144.04 (IV)(C), selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results.

> C. Changes in Sequence of Adding Ingredients
>
> *Ex parte Rubin* , 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render *prima facie* obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is *prima facie* obvious.).

However, Uraji et al do not teach the DSM 6601 strain, or the pMut plasmids, or use of a tetracylcine cassette in one of the plasmids.

Blum-Oehler et al (IDS ref., specifically pp. 59) teaches the E. coli strain, DSM 6601, which is also called Nissle 1917, which contain the pMut1 and pMut2 plasmids. However, they do not teach curing plasmids.

Trevors et al (FEMS Microbiol. Reviews 32: 149-157, 1986, specifically p. 149) teaches curing bacteria of plasmids.

Gasson et al (J. Bac. 154(1): 1-9, 1983, especially, p. 1, table 1 and figure 2) teaches curing a Streptococcus strain of five plasmids.

Alexeyev et al (Gene 160: 63-67, 1995, see entire reference) teach a tetracycline resistance cassette in a plasmid.

The ordinary skilled artisan, desiring to have a plasmid-free clone of DSM 6601, would have been motivated to combine the teachings of Uraji et al teaching how to cure bacteria of plasmids using the sacB gene with the teachings of Blum-Oehler et al teaching the DSM 6601 strain with the teachings of Alexeyev et al teaching a tetracycline cassette in a plasmid because Trevors et al teach that it is desirable to cure bacteria of plasmids because it allows for a direct comparison of cells with and without plasmids, and Gasson et al teach that a strain having more than one plasmid can pose problems in assignment of suspected plasmid-encoded phenotypes to individual molecules. It also complicates the analysis of plasmid transfer experiments, and the molecular study of individual plasmids from the complement. One further would be motivated to cure DSM 6601 because Blum-Oehler et al teach that DSM 6601 is useful as a probiotic drug against intestinal disorders and diseases, and, as taught by Blum-Oehler et al, their method is a much safer way of curing as it essentially has no effect on the host chromosome. It would have been obvious to one of ordinary skill in the art to use a tetracycline resistance cassette in one of the plasmids because Alexeyev et al teach that antibiotic-resistance gene cassettes are often used in vector construction. Furthermore, the recited elements are being used for their known and expected properties. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence

to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 10:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michele K. Joike/
Primary Examiner, Art Unit 1636

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